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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/077,572	10/13/98	APICELLA M	875001US2

HM12/0104
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1641	16

DATE MAILED: 01/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/077,572	Apicella et al.
Examiner	**Group Art Unit**
S. Devi, Ph.D.	1641

☒ Responsive to communication(s) filed on *Sep 3, 1999* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *22-26 and 29-31* is/~~are~~ pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *22-26 and 29-31* is/~~are~~ rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *15*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 09/03/99 (paper no. 13) in response to the Office Action mailed 04/28/99 (paper no. 11). With this, Applicants have amended the specification.

Status of Claims

2) The non-elected claims 33-35 and elected linking claims 36, 42 and 43 have been canceled.

Claims 22-26 and 29 have been amended.

New claims 30-31 have been added.

Claims 22-26 and 29-31 are pending and are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicants' Supplemental Information Disclosure Statement filed 09/03/99 (paper no. 15). One of the documents referred to therein has been considered and the other having incomplete citation is lined through. A signed copy of the IDS is attached to this Office Action (paper no. 16).

Declaration under 37 C.F.R § 1.132

4) Acknowledgment is made of Applicants' declaration filed 09/03/99 (paper no. 14) under 37 C.F.R § 1.132.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objections Withdrawn

7) The objection to the specification made in paragraph 7(a) of the Office Action mailed 04/28/99 (paper no. 11) is withdrawn in light of Applicants' amendment to the first paragraph of the specification to reflect the correct continuity status of the instant application.

8) The objection to the specification made in paragraph 7(b) of the Office Action mailed 04/28/99 (paper no. 11) with regard to a spelling error is withdrawn in light of Applicants' amendment of the specification.

Objection Maintained

9) The objection to the drawings made in paragraph 6 of the Office Action mailed 04/28/99 (paper no. 11) is maintained for reasons set forth therein. Applicants assure the Office that corrected formal drawings will be submitted upon notification of allowance of claims.

Rejections Withdrawn

10) The rejection of claims 23, 24 and 29 made in paragraph 11 of the Office Action mailed 04/28/99 (paper no. 11) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.

11) The rejection of claims 22, 23 and 25 made in paragraph 13 of the Office Action mailed 04/28/99 (paper no. 11) under 35 U.S.C. § 102(a) as being anticipated by Lee *et al.* (*J. Biol. Chem.* 270: 27151-27159, November 1995), is withdrawn in light of Applicants' declaration filed under 37 C.F.R § 1.132. Applicants state that the fifth co-author of the Lee's publication, Jeffrey J. Engstrom, is not an inventor.

12) The rejection of claims 24, 26 and 29 made in paragraph 15 of the Office Action mailed 04/28/99 (paper no. 11) under 35 U.S.C. § 103(a) as being unpatentable over Lee *et al.* (*J. Biol. Chem.* 270: 27151-27159, 1995) as applied to 22 and further in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992) is withdrawn in light of Applicants' declaration filed under 37 C.F.R § 1.132 stating that the fifth co-author of the primary reference of Lee *et al.*, Jeffrey J. Engstrom, is not an inventor.

13) The rejection of claim 29 made in paragraph 15 of the Office Action mailed 04/28/99 (paper no. 11) under 35 U.S.C. § 103(a) as being unpatentable over Lee *et al.* (*J. Biol. Chem.*

270: 27151-27159, 1995) as applied to claim 22, and further in view of Sprouse *et al.* (US 5,641,492) is withdrawn in light of Applicants' declaration filed under 37 C.F.R § 1.132 stating that the fifth co-author of the primary reference of Lee *et al.*, Jeffrey J. Engstrom, is not an inventor.

Rejections Maintained

14) The rejection of claims 22, 23, 25 and 29 made in paragraph 9 of the Office Action mailed 04/28/99 (paper no. 11) under the judicially created provisional obviousness type double patenting is maintained for reasons set forth therein. Applicants state that if appropriate, they will consider filing a terminal disclaimer upon notification of allowable subject matter.

15) The rejection of claims 22-26 and 29 made in paragraph 10 of the Office Action mailed 04/28/99 (paper no. 11) under 35 U.S.C. § 112, first paragraph, with regard to the deposit of the mutant bacterium is maintained for reasons set forth therein. Applicants assure the Office that upon receiving indication of allowable subject matter, Applicants will deposit plasmids pB28 and pB29 in compliance 37 C.F.R 1.801-1.809.

New Rejections

Applicants are asked to note the new rejections made in this Office Action. The Applicants' amendment including the addition of new claims, necessitated the new ground(s) of rejection presented in this Office Action.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

16) Claims 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 29 and 30 currently encompass a method for producing endotoxin-specific antisera by immunizing an individual with a vaccine formulation comprising **three** active ingredients, i.e., 1) An *htrB* mutant of a gram-negative bacterial pathogen; 2) An endotoxin isolated from the *htrB* mutant of the gram-negative bacterial pathogen **and,** 3) An endotoxin isolated from the *htrB*

mutant of the gram-negative bacterial pathogen wherein the endotoxin is conjugated to a carrier protein. However, there appears to be no support in the instant specification for such a method of producing an endotoxin-specific antisera using a three-component vaccine composition. Applicants have not pointed to the specific parts of the disclosure that support this added limitation in the claims. Therefore, the limitation in the claims is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation, or to remove the new matter from the claim.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

17) Claims 22-26 and 29-31 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 22 lacks antecedence for the recitation "**the wild type** gram-negative bacterial pathogen" (see lines 6 and 8) (Emphasis added), because the earlier occurrence of this recitation has been canceled via the amendment filed 09/03/99.

(b) Claims 29 and 30 lack antecedence for the recitation "**the wild type** gram-negative bacterial pathogen" (see part b).

(c) Claim 23 lacks proper antecedence for the recitation "**the** *htrB* mutant" (see line 3) (Emphasis added). Claim 23 depends from claim 22, which recites a "gram-negative bacterial pathogen" comprising a mutated *htrB* gene, but not a "*htrB* mutant".

(d) Claim 29 is vague, confusing and/or incorrect in reciting "immunizing an individual with a vaccine formulation comprising as an active ingredient an *htrB* mutant of a gram-negative bacterial pathogen, endotoxin isolated from the *htrB* mutant of the gram-negative bacterial pathogen, **and** endotoxin isolated from the *htrB* mutant of the gram-negative bacterial pathogen

wherein the endotoxin is conjugated to a carrier protein" (see part a of the claim) (Emphasis added). Note that the Markush language "selected from the group consisting of" (see line 5) has been removed via the amendment filed 09/03/99. As the claim is drafted currently, the vaccine formulation used to immunize an individual comprises three active ingredients: the mutant bacterium plus endotoxin of the mutant bacterium plus such endotoxin conjugated to a carrier protein. However, such a method of producing endotoxin-specific antisera by immunizing an individual with a vaccine formulation comprising **three** active ingredients is not supported by the instant specification.

(e) Analogous criticism as explained above in paragraph (d) applies to claim 30. Moot

(f) In claim 31, it is unclear how the step of using the mutant endotoxin to generate antibodies further limits the mutant endotoxin itself. Clarification is requested. Moot

(g) It is not clear what the differences are, if any, between the methods of claims 29 and 30, both of which contain identical steps. 30 Moot

(h) Claim 22 is confusing and/or incomplete because it is unclear how just "mutating an *htrB* gene within a gram negative bacterial pathogen" can lead to a "method of making a mutant endotoxin". The process of "mutating an *htrB* gene within a gram negative bacterial pathogen" would result in a mutated bacterium, not in a mutant endotoxin. Clarification is required.

Rejection under 35 U.S.C. § 102(b)

18) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejection under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19) Claim 22 is rejected under 35 U.S.C § 102(b) as being anticipated by Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992, already of record).

Karow *et al.* teach a method of making a mutant endotoxin or LPS from a Gram negative bacterial pathogen, *E. coli,* containing a mutated *htrB* gene. The mutant bacterium produces a mutant endotoxin lacking one or more lauric acid and myristic acid (i.e., secondary acyl chains of

lipid A) (see abstract; page 7413 left column; paragraph bridging left and right columns on page 7416, and page 7409, left column, under 'Fatty acid analysis'). The description provided in the Figure 4 legend indicates that the *htrB* mutant endotoxin is isolated from the *htrB* mutant bacterium (see page 7413). That the absence of one or more lauric acid and myristic acid in the lipid A renders the bacterial LPS substantially less toxic is inherent from the teachings of Karow *et al.*

Claim 22 is anticipated by Karow *et al.*

Rejection(s) under 35 U.S.C. § 103(a)

20) Claims 23-26 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Karow *et al.* (*J. Bacteriol.* 174: 7407-7418, 1992, already of record) as applied to claim 22 above, and further in view of Gupta *et al.* (*Infect. Immun.* 60: 3201-3208, 1992, already of record).

The teaching of Karow *et al.* is explained above which does not expressly disclose a method of purifying the mutant endotoxin by phenol-water extraction, or conjugating the mutant endotoxin to a carrier protein, or raising antisera to the mutant endotoxin in an individual.

However, the method of purifying an endotoxin, for example, by phenol-water extraction is conventional and is well known in the art for decades. See the section 'State of the Art' below.

Similarly, conjugating a substantially less toxic endotoxin of a gram negative bacterial pathogen to a carrier protein to enhance the immunogenicity of the endotoxin is widely practiced in the art. For instance, Gupta *et al.* teach conjugating a deacylated endotoxin of a Gram negative bacterial pathogen to a protein carrier to produce an immunogenic conjugate vaccine that can be used to raise endotoxin-specific antisera by administering it to an individual animal (see abstract, and pages 3202 and 3203).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to purify Karow's mutant endotoxin lacking one or more myristic acid substitutions in the lipid A using the conventional art-known phenol-water extraction and conjugate the resultant purified mutant endotoxin to a carrier protein to raise endotoxin-specific antisera as taught by Gupta *et al.* One skilled in the art would have had a reasonable expectation of success in producing the purified mutant endotoxin and the conjugate for use as a vaccine formulation, or as

an immunogen to raise endotoxin-specific antisera of the instant invention, since the *htrB* mutant endotoxin lacking secondary acyl chains is expected to function significantly no differently in a conjugate than the deacylated endotoxin taught by Gupta *et al.* Absent evidence to the contrary, claims 23-26 and 31, as a whole, are obvious over the prior art of record.

Objection

21) Claim 30 is grammatically incorrect in the recitation "comprising an active ingredient an htrB mutant" (see lines 3 and 4). Moot

Remarks

22) Claims 22-26 and 29-31 stand rejected.

23) The prior art made of record and not relied upon currently in any rejection is considered pertinent to Applicants' disclosure:

- Westphal *et al.* (*Methods Carbohydr. Chem.* 5: 83-91, 1965) teach phenol water extraction of gram negative bacterial lipopolysaccharides (see entire document).
- Karow ML. Molecular Genetics of the *Escherichia coli htrB* gene. Ph.D. Dissertation, The University of Utah, 1992.
- McLaughlin *et al.* (*J. Bacteriol.* 174: 6455-6459, 1992) teach a method of preparing an endotoxin derived from a gram negative bacterial mutant using microphenol method and proteinase K treatment (see page 6456, left column).

24) THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date

of this final action.

25) Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1 (CM1). The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m to 4.00 p.m.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January 2000

James C. Housel
JAMES C. HOUSEL 1/3/00
SUPERVISORY PATENT EXAMINER